

## Non-Technical Abstract

Human immunodeficiency virus (HIV) productively infects human CD4<sup>+</sup> cells, including CD4<sup>+</sup> T cells, cells of the monocyte/macrophage lineage, and other cell types, such as neuronal cells and causes their progressive depletion. Infection with HIV usually progresses from initial seroconversion to apparent clinical latency, followed by progressive immunodeficiency, opportunistic infections, malignancies, and death. Depletion of CD4<sup>+</sup> cells results from the combined direct cytopathic effects of HIV-1 and from inappropriate auto-immune destruction of uninfected CD4<sup>+</sup> cells. Both destructive processes appear to be the result, at least in part, of cellular exposure to the HIV-1 envelope glycoprotein, gp120.

Over a decade after the first description of AIDS was reported, the global pandemic continues to grow. This, combined with emerging concerns of the limited effectiveness of primary anti-viral agents such as reverse transcriptase inhibitors demands that innovative therapies be developed including gene therapy based strategies. We have shown that human CD4<sup>+</sup> T-cell lines transduced with a intracellular human single chain antibody against the HIV-1 envelope glycoprotein, termed sFv105, are protected from the cytopathic effects of HIV-1. Moreover, the infectivity of the HIV-1 particles produced by cells that express sFv105 is substantially reduced. Cell-surface phenotype, replication rate, morphology, and response to mitogenic stimulation of the transduced cells are also normal.

In this study, we will evaluate the safety and efficacy of intracellular antibody gene therapy in six asymptomatic patients with HIV-1 infection by reinfusing autologous CD4<sup>+</sup> T cells that have been engineered *ex vivo* with a retroviral vector that expresses the sFv105 antibody. The *in vivo* survival of sFv105-expressing cells will be compared by limiting dilution PCR with those of a separate aliquot of cells engineered with a control vector (identical except for the sFv105 gene). The level and persistence of sFv105 expression and various immunologic parameters including CD4 counts, virus load and cytotoxic T-cell activity will be assessed. The results will determine whether this intracellular antibody can protect CD4<sup>+</sup> T cells in patients with HIV-1 infection. The results will also aid in the design of future trials of larger scale T cell replacement and of hematopoietic stem cell gene therapies of HIV disease.